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Original Article

Prognostic factors in advanced breast cancer: Race and receptor status are significant after development of metastasis

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ABSTRACT

Prognostic factors are well established in early-stage breast cancer (BC), but less well-defined in advanced disease. We analyzed 323 BC patients who had distant relapse during follow-up from 1997 to 2010 to determine the significant clinicopathologic factors predicting survival outcomes. By univariate analysis, race, tumor grade, estrogen and progesterone receptors (ER/PR) and HER2 status were significantly associated with overall survival (OS) and post-metastasis survival (PMS). Applying a Cox regression model revealed that all these factors remained significant for PMS, while race, tumor grade and HER2 were independent factors for OS. Tumor grade was the only significant factor for metastasis-free survival by univariate and multivariate analyses. Our findings demonstrated that being Caucasian, hormonal receptor positive (HR+) and HER2 positive (HER2+) were all associated with a decreased hazard of death and that patients with HR+/HER2+ tumors had superior outcomes to those with HR+/HER2− disease. Further, PR status held a prognostic value over ER, thus reflecting the biologic mechanism of the importance of the functional ER pathway and the heterogeneity in the response to endocrine therapy. These observations indicate that the patients' genetic makeup and the intrinsic nature of the tumor principally govern BC progression and prognosticate the long-term outcomes in advanced disease.

Introduction

Breast cancer is the most common malignancy and the second leading cause of cancer mortality among American women, with 232,670 estimated new cases in 2014 [1]. This represents close to 30% of all new cancer cases in women. Approximately 20% of breast cancer patients develop metastasis either at initial presentation or subsequently [2]. Distant recurrence dramatically worsens the prognostic outcome, as 90% of breast cancer mortality is the result of relapses at distant sites that are resistant to adjuvant therapies [3].

Despite the introduction of more effective therapeutic modalities in the past few decades, the overall median survival in stage IV breast cancer remains low, ranging from 15–27 months [4–6]. However, advanced breast cancer comprises a heterogeneous group of diseases with a disparate clinical course, thus reflecting the biologic heterogeneity of this malignancy. Therefore, assessing the clinicopathologic factors with prognostic significance in this group of patients is crucial in pursuing personalized management strategies to achieve the finest clinical outcomes.

Previous studies have identified a broad range of clinicopathologic factors with prognostic significance in early-stage breast cancer, including age, race, tumor type, grade and size, lymphovascular invasion and axillary nodal status, with the latter being arguably the most powerful prognosticator [7–14]. Hormonal receptor (estrogen/progesterone receptor, ER/PR) and HER2 status have long been considered as strong predictive markers. While ER/PR-positive tumors are generally associated with a prolonged disease-free and overall survival in the absence of adjuvant systemic therapy [15], the prognostic value of hormone receptor status tends to recede with time [16]. HER2 overexpression and/or amplification is typically associated with high grade tumors and yields an unfavorable prognosis, especially in patients untreated with HER2-targeted agents or chemotherapy [17,18]. The added value of its prognostic power in clinical practice becomes questionable as the outcomes may have been heavily influenced by the administration of HER2-directed therapy. While the addition of Trastuzumab, a monoclonal antibody against HER2, was associated with a prolonged disease-free and overall survival in HER2-positive, early-stage breast cancer patients [19], the prognostic significance

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of HER2 status of the primary tumor remains controversial in the metastatic setting in limited studies [20,21], and the survival benefit of HER2-targeted therapy with Trastuzumab does not appear to persist long-term in this subset of patients [21,22].

Most of the previous cohorts, however, focused on early-stage breast cancers. Those that examined advanced breast cancer mostly combined the patients with distant relapse after follow-up and those with metastasis at the time of presentation [6,2,23–28], of which the latter is associated with the worse prognosis [29]. In this study, we sought to seek which clinicopathologic factors linked to the primary tumors were significantly associated with survival outcomes in a cohort of breast cancer patients who developed advanced disease during follow-up.

Materials and methods

This retrospective study was performed after approval by the University of Alabama at Birmingham Institutional Review Board. The UAB Tumor Registry was searched to identify breast cancer cases with associated distant organ (bone, visceral organs and brain) metastasis between 1997 and 2010. Those patients who were male, had locoregional recurrence or lymph node metastasis without distant relapse or had metastatic disease at presentation were excluded. The patients' demographic information and the pathologic features of the primary tumor were recorded, including age, race, tumor type, tumor size, histologic grade, the number of positive axillary lymph nodes along with ER, PR and HER2 status. The accuracy of the data was further verified for each patient using the electronic medical record. Given the arguable prognostic significance of ER, PR and HER2, the patients without any recorded receptor status were also excluded from the study. This led to a total of 323 cases meeting the inclusion criteria.

All patients received surgical treatment and systemic therapy (endocrine therapy, targeted therapy, cytotoxic chemotherapy, or their combination). One hundred and fourteen of 200 patients with hormonal receptor-positive (HR+; ER+and/or PR+) disease received endocrine therapy at the authors' institution based on physician and patient discussions. While a significant proportion of patients with HR+ disease were recommended for endocrine therapy, they did not receive anti-estrogen therapy at the authors' institution. A small subset of patients (23/123, 19%) with HER2-positive (HER2+) disease received HER2-targeted therapy with Trastuzumab at the authors' institution. All but 50 patients with HR+ disease and 37 of 45 patients with ER−/PR−/HER2+ tumors received cytotoxic chemotherapy.

The ER and PR expression was assessed by immunohistochemistry, and HER2 status was examined by immunohistochemistry or fluorescence/chromogenic *in situ* hybridization as previously described [21]. A positive ER or PR was defined as ≥1% of tumor cell nuclei with immunoreactivity. HER2 overexpression/gene amplification was determined as either a 3+ immunohistochemistry score (uniform and intensity membrane staining of >30% of tumor cells) or a positive *in situ* hybridization result. When the receptor (ER, PR or HER2) status was not recorded in the Tumor Registry or in the medical chart, the patient was coded as having unknown receptor status for that particular receptor.

The subtype classification of breast cancer was based on results of HR/HER2 status as previously reported [30]. In brief, tumors were defined as luminal (ER+ and/or PR+), HER2 (ER−/PR−/HER2+) or triple negative (ER−/PR−/HER2−). The luminal carcinomas were further separated into HR+/HER2− and HR+/HER2+. Although a subset of triple-negative tumors represents basal-like cancers, this group was not further subclassified.

Statistical analysis

Overall survival (calculated from the date of diagnosis to the date of death from any cause or the follow-up cutoff), metastasis-free survival (from the date of diagnosis to the date of distant organ relapse), and post-metastasis survival (from the date of distant organ relapse to the date of death) were mapped on Kaplan–Meier curves. Patients who survived or were lost to follow-up were considered as censored data in the analysis. The Log-Rank test was used to compare groups. The Cox proportion hazard models were utilized to determine an association between the survival and all other tested factors. A *P*-value of 0.05 or less was considered statistically significant. Statistical analysis was performed by utilizing SAS v9.1 software (SAS Institute Inc., Cary, North Carolina).

Results

Clinicopathological characteristics

The demographic information of the 323 patients included in the study and pathologic characteristics of the primary tumor

Table 1
Patients' demographics and pathologic characteristics of the primary tumors.

Characteristics	No. of patients (%)
Age	
<40	60 (19)
40–49	103 (32)
50–59	89 (27)
≥60	71 (22)
Race	
African American	87 (27)
Caucasian	236 (73)
Tumor type	
Ductal	281 (87)
Lobular	15 (5)
Ductal and lobular	20 (6)
Others[a]	7 (2)
Tumor grade	
I	16 (5)
II	85 (26)
III	200 (62)
Unknown	22 (7)
Tumor size	
≤2	76 (24)
>2, ≤5	94 (29)
>5	38 (12)
Unknown	115 (35)
Number of positive nodes	
0	56 (18)
1–3	71 (22)
4–9	49 (15)
≥10	33 (10)
Unknown	114 (35)
ER	
Negative	123 (38)
Positive	187 (58)
Unknown	13 (4)
PR	
Negative	163 (50)
Positive	144 (45)
Unknown	16 (5)
HER2 amplification/overexpression	
Negative	161 (50)
Positive	123 (38)
Unknown	39 (12)

[a] Including 3 inflammatory carcinomas, 3 mucinous carcinomas, and 1 metaplastic carcinoma.